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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/485,601	05/04/00	STRITTMATTER S	OCR-842

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1652	9

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/485,601	Applicant(s) Strittmatter
	Examiner Kathleen Kerr	Group Art Unit 1652

☒ Responsive to communication(s) filed on *11/13/00* .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-20* is/are pending in the application.

Of the above, claim(s) *3-5, 14-16, and 18-20* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1, 2, 6-13, and 17* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☒ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *6*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Application Status

1. In response to the restriction requirement (Paper No. 7), Applicants filed a reply on November 13, 2000.

Claims 1-20 are pending in the instant application.

Election

2. Applicant's election with traverse of Group I, Claims 1, 2, 6-13, and 17 in Paper No. 8 is acknowledged. The traversal is on the ground(s) that the three Groups do **not** provide three distinct inventive concepts because "there is a technical relationship among the claimed inventions, as they all are related to the use of rho protein inhibitors to promote axon regeneration...no matter what the route of administration". This is not found persuasive because the technical feature which joins Groups I and II, namely the inhibitors, and particularly C3 exoenzyme, is not a special technical feature because said feature is not novel. Thus, the different routes of administration, either directly administering the C3 exoenzyme or administering a virus encoding the C3 exoenzyme so that said exoenzyme will be expressed and, thus, indirectly administered, lack unity of invention. Furthermore, Group III is merely a rho inhibitor assay which lacks novelty in view of the prior art (see International Search Report), and thus also does not share a special technical feature, which feature must be novel.

Applicant's traversal is also on the grounds that the International Search Report does not hold a lack of unity of the instant claims. This is not found persuasive because restriction according to U.S. restriction practice or international, lack of unity practice, is at the discretion of the Examiner (see 37 CFR 1.499 in MPEP 1893.03(d)). The Examiner did not hold a lack of unity in the international application; however, adequate reasoning for lack of unity has been set forth in the previous Office action.

Applicant's traversal is also on the grounds that no search burden would be required of the Examiner to examine all the claims of the instant application. The Examiner disagrees. The search for direct protein administration involves a search for the protein while a search for virus-encoding administration involves a search for encoding DNAs; such a search is not co-extensive in either the patent literature, having distinct class/subclass classifications, or in the non-patent literature where proteins are often disclosed without benefit of either amino acid or DNA sequence.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1, 2, 6-13, and 17 will be examined as they pertain to directly administering a pharmaceutical composition that is the rho inhibitor and **not** as they pertain to methods of gene therapy using, as a pharmaceutical composition, a virus encoding said inhibitor. Claims 3-5, 14-16, and 18-20 are withdrawn from consideration as pertaining to non-elected inventions.

Priority

3. Applicant is granted the benefit of priority for the provisional application 60/055,268 filed on August 13, 1997 and the internationally filed application PCT/US98/16794 filed on August 12, 1998 as requested in the declaration. The filing date of said provisional application is less than 30 months prior to Applicant's request under 35 U.S.C. 371 for the international application.

The Examiner notes that the subject matter of Claims 8 and 17 was not disclosed in the provisional application and, thus, is granted a priority date of August 12, 1998 for the international filing. The subject matter of all other claims was disclosed in the provisional application and, thus, is granted a priority date of August 13, 1997 for the provisional application.

Information Disclosure Statement

4. The information disclosure statement filed on June 19, 2000 has been reviewed, and its references have been considered as shown by the Examiner's initials next to each citation on the attached copy.

Drawings

5. The drawings are considered informal for the reasons detailed in the attached copy of PTO Form 948. Appropriate correction is required prior to allowance.

Objections to the Specification

6. The title is objected to for not being adequately descriptive of the instant subject matter. The Examiner suggests inserting rho inhibitors or *C. botulinum* C3 exoenzyme into the title.

7. The specification is objected to because this application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

8. The specification is objected to for lacking specificity. On page 13, lines 20-28, particular amino acid residues of a protein, rho, are described; however, Applicant provides no sequence information in the form of a sequence listing or a particular GenBank Accession number or even a careful definition of the protein, rho (for example, by including the species). Appropriate correction is required.

9. The specification is objected to for the use of abbreviations which are not defined.

a. On page 3, line 19, the term "DRG neurons" is used; the term DRG is used throughout the specification without definition.

b. On page 4, line 8, "*C. botulinum*" is used; the species *C. botulinum* is used throughout the specification without definition of the "C" which, the Examiner assumes, is *Clostridium*.

c. On page 15, line 14, the term "TPA" is used without definition.

d. On page 20, line 20, the term "CRMP" is used without definition.

Appropriate definition of these abbreviations is required.

Objections to the Claims

10. Claims 1, 2, 6-11 are objected to for containing non-elected subject matter. The parent Claim 1 must be rewritten so that the instant claims are only drawn to the direct administration of a protein composition to a patient.

11. Claim 6 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The parent Claim 1 utilizes rho inhibitors while the instant Claim 6 utilizes not only rho inhibitors but also rac and cdc42 inhibitors thus broadening the scope in the dependent claim. See also the 112, second paragraph rejection below (section 12).

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 1-2, 6, and 9-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In the instant specification, rho inhibitors are described as many things (see instant specification, page 10) including inhibitors of rac, cdc42, or other

proteins in the GTP-binding family. Thus, the metes and bounds of the term "rho inhibitor" are unclear, particularly in light of the dependent Claim 6.

13. Claims 8 and 17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "C2/C3 inhibitor" is unclear. In the art, the *C. botulinum* C2 toxin has two components, I and II (see Barth et al.). While the specification teaches using a portion of C2, it fails to define which component of C2 is useful. Barth et al. teach using the N-terminus of component I is methods such as those taught by Applicant.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

14. Claims 1, 2, and 6-11 are rejected under 35 U.S.C. 112, first paragraph, enablement, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The instant claims are drawn to methods of growing CNS axons in a patient by treating said patient with a rho protein inhibitor, more specifically with the *C. botulinum* C3 exoenzyme. The instant application has not enabled the scope of the use of *any* rho

protein inhibitor in said methods, the instant application has not enabled the scope of the use of an undefined chimera of C2/C3 toxins in said methods, and the instant application has not enabled the use of *C. botulinum* C3 exoenzyme in the claimed methods. Thus, the entire scope of the claimed methods is not enabled for promoting CNS axon growth.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

Firstly, the Examiner will address the issue of scope pertaining to enablement of the instant claims using a rho protein inhibitor other than C3 exoenzyme. The instant specification provides a single example of a rho protein inhibitor for use in the claimed methods, the C3 exoenzyme from *C. botulinum*. While experimentation to determine other inhibitors of rho protein is not without direction, the instant specification provides no suggestion that administration of any other rho protein inhibitor will promote CNS axon growth. The state of the art is such that nerve growth and/or regeneration is a complex process in which "multiple inhibitory proteins exist, and, for efficient axon regeneration in adult CNS, it will be important to neutralize their inhibitory effects" (see Lehmann et al. IDS, page 7537, first paragraph). Thus, the unpredictability in using other rho protein inhibitors limits the scope of the claims which may enabled by the instant specification. This same argument extends to the use of an undefined chimera of C2/C3 exoenzyme since Applicant's examples are directed at the full-length C3 exoenzyme and the C2/C3 exoenzyme chimera need not contain the entire C3 exoenzyme.

Secondly, the Examiner will address the issue of enablement (of the entire scope) to the instant claims of methods using particularly C3 exoenzyme. The instant specification and the prior art support the teaching that axon/neurite growth is generated by *in vitro* treatment of neurons with C3 exoenzyme from *C. botulinum* (see Tigyi et al. and Kozma et al.). Particularly, the specification offers an example using dorsal root ganglia (DRG) neurons *in vitro* (see instant specification, Example 1). However, the response of DRG neurons to treatment is **not** indicative of CNS neurons. The distinct difference between peripheral (which is DRG) axon growth and

CNS axon growth or regeneration is well documented (see review by Jackowski); thus, treatments which affect growth in peripheral nerves (like DRG) are not predictably likely to affect growth in CNS nerves. Applicant supports enablement of the growth of CNS neurons in Example 2 in which C3 exoenzyme is administered using a virus; the effective administration to DRG neurites is not representative of CNS axon growth, as reasoned above, and the administration to rat brain is not tested for effectiveness, but only for administration. Thus, the methods using C3 exoenzyme have not been shown to promote CNS axon growth by the instant specification. Furthermore, the unpredictability of the art in this field is extensive. The state of the art indicates that the ability to grow CNS axons has not been shown (see Jackowski et al.), and to enable such claims, Applicant must show definitive evidence or likelihood of such growth. Applicant has provided no working examples of CNS axon growth as a result of treatment with C3 exoenzyme. While screening for such growth is clear, the predictability of finding an effective compound is very low in consideration of the art at the time of the invention. In summary, neither using any rho inhibitor nor using C3 exoenzyme in the instant methods is enabled by the instant specification to promote CNS axon growth.

15. Claims 1-2, 6, and 9-12 are rejected under 35 U.S.C. 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant claims are directed to

methods using rho protein inhibitors; the instant specification defines rho protein inhibitors as any inhibitor of rho protein function such as small molecules (inferred), proteins which inactivate rho (such as C3 exoenzyme), analogues that bind rho receptors, antibodies, inhibitors of rho protein synthesis or stability, or any inhibitor of rac, cdc42, or other proteins in the GTP-binding family. In essence, such a description is a function description of a chemical species, and where said chemical species is an encoded protein, such a description is a functional description of genetic material. The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original).

Just as the claims at issue in UC v. Lilly defined the invention by the function of the claimed DNA (encoding insulin), the inhibitors used in the instant claims are defined only by their functional properties. The Court held this sort of functional definition insufficient. "In claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly such a formula is normally an adequate description of the claimed genus. In claims to methods using genetic material, however, a generic statement such as 'vertebrate insulin cDNA' or 'mammalian insulin cDNA,'

without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is" in UC v. Lilly, at *24-*25.

Applicant has not described a representative number of species in such a broad genus because, using only the one described species, one of skill in the art could not reasonably predict the structure of other species encompassed by the claimed genus.

Claim Rejections - 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

16. Claims 12 and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Morii et al. The instant claims are drawn to a pharmaceutical composition comprising *C. botulinum* C3 exoenzyme and a pharmaceutically acceptable carrier, such as Tris-HCl.

Morii et al. teach a purified preparation of *C. botulinum* C3 exoenzyme in 50 mM Tris-HCl, pH 7.5 and 0.2 M NaCl (see Abstract and page 770, right column, first full paragraph). Such a preparation meets the limitations of Applicant's claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. Claim 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over Barth et al. in view of Morii et al. The instant claim is drawn to a pharmaceutical composition comprising *C. botulinum* C2/C3 chimera and a pharmaceutically acceptable carrier, such as Tris-HCl.

Barth et al. teach a C2/C3 chimera wherein the C2 portion is identical to Applicant's composition, but the C3 portion is taken from a different C3 toxin, a C3-like exoenzyme from *C. limosum* which inactivates Rho by ADP-ribosylation (see page 1364, right column, second paragraph). The chimera taught by Barth et al. is stored in PBS (see page 1365, right column,

first full paragraph) and is used in cell culture treatments (see page 1365, right column, fourth full paragraph) and, thus, contains a pharmaceutically acceptable carrier.

Morii et al. teach, as described above, and that the C3 exoenzyme from *C. botulinum* inactivates Rho by ADP-ribosylation.

It would have been obvious to modify the teachings of Barth et al. and produce a C2/C3 chimera using the C2 piece taught by Barth et al. and the C3 exoenzyme taught by Morii et al. (in place of the C3-like exoenzyme from *C. linosum* taught by Barth et al.) because the C3 piece used by Barth et al. and the C3 exoenzyme taught by Morii et al. are identical functional units, both toxin polypeptides with ADP-ribosylation activity which inactivates Rho. One would have been motivated to produce such a chimera because C3 and "C3-like toxins have been valuable tools for the elucidation of the function of Rho GTPases" while "the use of C3 and C3-like transferases is hampered by the fact that these enzyme do not enter cells readily" (see Barth et al., page 1364, right column, second paragraph). Thus, one of ordinary skill in the art would have used the teachings of Barth et al. to produce a C3 exoenzyme from *C. botulinum* which more readily enters cells.

Conclusion

18. No claims are allowed in the instant application for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Dr. Kathleen M. Kerr whose telephone number is (703) 305-1229. The Examiner can normally be reached on Monday to Friday from 8:30 a.m. to 5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Mr. Ponnathapura Achutamurthy, can be reached on (703) 308-3804. The fax phone number for this Group is (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

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